	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Errors
1	BRS	L1	1935	thrombin adj inhibitor	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/24 16:35			0
2	BRS	L2	107	(thrombin adj inhibitor) same prodrug	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/24 16:35			0
3	BRS	L3	2	kit same 2	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/24 16:43			0
4	BRS	L4	0	(pharmaceutical adj composition) same 2	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/24 16:45			0
5	BRS	L5	21	melagatran	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/24 16:43			0
6	BRS	L6	6	melagatran same prodrug	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/24 16:44			0
7	BRS	L7	2	6 same (kit or composition)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/24 16:44			0
8	BRS	L8	1	(composition) same 2	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/24 16:45			0
9	BRS	L9	5	(((thrombin adj inhibitor) same prodrug) or (melagatran same prodrug)) same (composition or formulation)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/24 16:46			0

	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Errors
1	BRS	L1	2	kit same ((thrombin adj inhibitor) same prodrug)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/24 16:56			0
2	BRS	L2	107	(thrombin adj inhibitor) same prodrug	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/24 16:56			0
3	BRS	L3	6	melagatran same prodrug	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/24 16:57			0
4	BRS	L4	5299	(venous adj thrombosis) or (pulmonary adj embolism) or (disseminated adj intravascular adj coagulation)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/24 16:58			0
5	BRS	L5	1	4 same (2 or 3)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/24 16:58			0

=> d his

(FILE 'HOME' ENTERED AT 16:48:24 ON 24 NOV 2002)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
16:48:53 ON 24 NOV 2002
L1 10243 S THROMBIN INHIBITOR
L2 50 S L1 (P) PRODRUG
L3 0 S L2 (P) (KIT OR COMPOSITION)
L4 29 S MELAGATRAN (P) PRODRUG
L5 1 S L4 (P) (KIT OR COMPOSITION OR FORMULATION)
L6 309321 S THROMBOSIS OR (PULMONARY EMBOLISM) OR (DISSEMINATED INTRAVASC
L7 14 S L6 (P) (L2 OR L4)
L8 9 DUPLICATE REMOVE L7 (5 DUPLICATES REMOVED)

=> log y

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FILE 'HOME' ENTERED AT 16:48:24 ON 24 NOV 2002

=> file medline caplus biosis embase scisearch agricola
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                               0.21       0.21

FILE 'MEDLINE' ENTERED AT 16:48:53 ON 24 NOV 2002

FILE 'CAPLUS' ENTERED AT 16:48:53 ON 24 NOV 2002
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FILE 'EMBASE' ENTERED AT 16:48:53 ON 24 NOV 2002
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FILE 'SCISEARCH' ENTERED AT 16:48:53 ON 24 NOV 2002
COPYRIGHT (C) 2002 Institute for Scientific Information (ISI) (R)

FILE 'AGRICOLA' ENTERED AT 16:48:53 ON 24 NOV 2002

=> s thrombin inhibitor
L1        10243 THROMBIN INHIBITOR

=> s l1 (p) prodrug
L2           50 L1 (P) PRODRUG

=> s l2 (p) (kit or composition)
L3            0 L2 (P) (KIT OR COMPOSITION)

=> s melagatran (p) prodrug
L4           29 MELAGATRAN (P) PRODRUG

=> s l4 (p) (kit or composition or formulation)
L5            1 L4 (P) (KIT OR COMPOSITION OR FORMULATION)

=> d l5 1 ibib abs

L5   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:         2000:772474  CAPLUS
DOCUMENT NUMBER:          133:340244
TITLE:                    A pharmaceutical formulation comprising a low
                          molecular weight thrombin inhibitor and its prodrug
INVENTOR(S):              Gustafsson, David
PATENT ASSIGNEE(S):       Astrazeneca AB, Swed.
SOURCE:                   PCT Int. Appl., 30 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  ---------      ---------------  --------
     WO 2000064470      A1   20001102       WO 2000-SE756    20000419
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR,
             CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,
             ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,
             LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE,
             SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA,
             ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,
             DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
             CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     SE 9901442         A    20001022       SE 1999-1442     19990421
     BR 2000009847      A    20020108       BR 2000-9847     20000419
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     EP 1200118        A1   20020502       EP 2000-928047   20000419
        R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
            IE, SI, LT, LV, FI, RO, MK, CY, AL
     NO 2001005107     A    20011019       NO 2001-5107     20011019
PRIORITY APPLN. INFO.:                    SE 1999-1442     A  19990421
                                          SE 1999-4419     A  19991203
                                          WO 2000-SE756    W  20000419
OTHER SOURCE(S):         MARPAT 133:340244
AB   A pharmaceutical   ***formulation***   contains a low mol. wt. thrombin
     inhibitor, or a pharmaceutically acceptable deriv. with an adjuvant,
     diluent or carrier; a pharmaceutical   ***formulation***   including a
       ***prodrug***   of a low mol. wt. thrombin inhibitor, or a deriv. of that
       ***prodrug***  , in admixt. with an adjuvant, diluent or carrier.  The
       ***formulation***   is suitable for administration in the treatment of a
     condition in which the inhibition of thrombin is required.  A controlled,
     randomized, parallel group, Swedish multi-center pilot study was carried
     out.  The study was open with regard to the drugs under evaluation but was
     blind for the patients, all personnel at the study sites, and for the
     person monitoring the expts. with regard to the doses of
       ***melagatran***   and the   ***prodrug***   of   ***melagatran***  ,
     EtOOC-CH2-(R)Cgl-Aze-Pab-OH (I).  A combination of s.c. administered
       ***melagatran***   and orally administered I is effective in preventing
     venous thrombosis after orthopedic surgery.
REFERENCE COUNT:         4     THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT


=> d his

     (FILE 'HOME' ENTERED AT 16:48:24 ON 24 NOV 2002)

     FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
     16:48:53 ON 24 NOV 2002
L1         10243 S THROMBIN INHIBITOR
L2            50 S L1 (P) PRODRUG
L3             0 S L2 (P) (KIT OR COMPOSITION)
L4            29 S MELAGATRAN (P) PRODRUG
L5             1 S L4 (P) (KIT OR COMPOSITION OR FORMULATION)

=> s thrombosis or (pulmonary embolism) or (disseminated intravascular coagulation)
L6       309321 THROMBOSIS OR (PULMONARY EMBOLISM) OR (DISSEMINATED INTRAVASCULA
                R COAGULATION)

=> s L6 (p) (l2 or l4)
L7           14 L6 (P) (L2 OR L4)

=> duplicate remove l7
DUPLICATE PREFERENCE IS 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L7
L8             9 DUPLICATE REMOVE L7 (5 DUPLICATES REMOVED)

=> d l8 1-9 ibib abs

L8   ANSWER 1 OF 9  CAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:        2002:879541  CAPLUS
TITLE:                   Oral-direct thrombin inhibitors
AUTHOR(S):               Crowther, Mark A.
CORPORATE SOURCE:        McMaster University, Hamilton, ON, Can.
SOURCE:                  Fundamental and Clinical Cardiology (2003), 46(New
                         Therapeutic Agents in Thrombosis and Thrombolysis (2nd
                         Edition)), 265-271
                         CODEN: FCCAEH; ISSN: 1067-5264
PUBLISHER:               Marcel Dekker, Inc.
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   Current strategies for the treatment and prevention of venous
       ***thrombosis***   require a mix of parenteral and oral therapies that
     frequently require lab. monitoring.  Oral-direct   ***thrombin***
       ***inhibitors***   have the potential to simplify antithrombotic therapy;
     these agents produce a predictable anticoagulant response so that lab.
     monitoring may be unnecessary.  Ximelagatran, the oral direct
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thrombin ***inhibitor*** in the most advanced stage of development, is a ***prodrug*** of ***melagatran*** an active-site-directed inhibitor of thrombin. In phase II studies, ximelagatran has been evaluated as thromboprophylaxis in patients undergoing elective hip or knee replacement surgery and in patients with nonvalvular atrial fibrillation. The drug has also been studied in patients with acute venous ***thrombosis*** . In each case, ximelagatran appears to be at least as safe and effective as current antithrombotic interventions. Phase III studies with ximelagatran for these indications are currently underway. If ximelagatran lives up to its initial promise, it has the potential to revolutionize the prevention and treatment of ***thrombosis*** .

L8 ANSWER 2 OF 9 MEDLINE
ACCESSION NUMBER: 2002416506 MEDLINE
DOCUMENT NUMBER: 22161009 PubMed ID: 12170516
TITLE: [Prophylaxis of postoperative thromboembolism. New alternatives to low-molecular-weight heparin]. Profylax mot postoperativ tromboembolism. Nya alternativ till lagmolekylart heparin.
AUTHOR: Bergqvist David; Siegbahn Agneta
CORPORATE SOURCE: Avdelningen for klinisk kemi, Akademiska sjukhuset, Uppsala.. david.bergqvist@kirurgi.uu.se
SOURCE: LAKARTIDNINGEN, (2002 Jul 11) 99 (28-29) 3039-41. Journal code: 0027707. ISSN: 0023-7205.
PUB. COUNTRY: Sweden
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Swedish
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 20020813
Last Updated on STN: 20020914
Entered Medline: 20020913
AB For somewhat more than a decade low molecular weight heparins have dominated in the pharmacological prevention of postoperative venous thromboembolism. At present there are some new methods of potential interest both as prophylactic substances but also to better understand the pathophysiology of deep vein ***thrombosis*** . These are inhibition of factor VII a/tissue factor complex (NAP, Nematode Anticoagulant Protein), inhibition of activated factor X (the synthetic pentasaccharide fondaparinux) and thrombin inhibition (***melagatran*** and its oral ***prodrug*** ximelagatran). They have been shown to be effective in high risk orthopaedic surgery. They have to show their place in the prophylactic arsenal in comparison with low molecular weight heparins (effect, safety, mode of administration, cost-effectiveness).

L8 ANSWER 3 OF 9 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2002388952 IN-PROCESS
DOCUMENT NUMBER: 22132572 PubMed ID: 12137410
TITLE: BIBR-1048 Boehringer Ingelheim.
AUTHOR: Mungall Dennis
CORPORATE SOURCE: The Miami Project to Cure Paralysis, Department of Neurological Surgery, University of Miami School of Medicine, Lois Pope Life Center, FL 33101, USA.. Thertch@aol.com
SOURCE: Curr Opin Investig Drugs, (2002 Jun) 3 (6) 905-7. Journal code: 100965718. ISSN: 1472-4472.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20020725
Last Updated on STN: 20020725
AB BIBR-1048, a ***thrombin*** ***inhibitor*** and an orally-active ***prodrug*** of BIBR-953ZW, is under development by Boehringer Ingelheim as a potential antithrombotic agent [331881]. By 1999, BIBR-1048 was in phase II clinical trials for thromboembolism and the prevention of stroke due to atrial fibrillation [331881]; by April 2002, proof-of-principle had been demonstrated in phase II trials in deep vein ***thrombosis*** [446554]. In July 2001, the company revealed that an IND was expected to be filed for BIBR-953ZW in 2002 [415884].

L8 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:[redacted]154 CAPLUS
DOCUMENT NUMBER: 135:371637
TITLE: Synthesis of thiochromane derivatives for use as thrombin inhibitors
INVENTOR(S): Andersson, Kjell; Inghardt, Tord; Karlsson, Olle; Linschoten, Marcel; Nystroem, Jan-erik; Sunden, Gunnel
PATENT ASSIGNEE(S): Astrazeneca AB, Swed.
SOURCE: PCT Int. Appl., 93 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001087879	A1	20011122	WO 2001-SE1052	20010514

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: SE 2000-1803 A 20000516
OTHER SOURCE(S): MARPAT 135:371637
GI

/ Structure 1 in file .gra /

AB Synthesis of thiochromane derivs. (I) (R1 = halo; R2 = H, halo, alkoxy; Y = S=O, SO2) for use as ***thrombin*** ***inhibitors*** is disclosed. Thus, I (R1 = Cl, R2 = H, Y = SO2) (II) is prepd. in 8 steps from 4-chloro-2-methoxythiophenol, Et bromopropanoate and paraamidinobenzylamino azetidinecarboxylate. II in thrombin clotting time assay shows an IC50TT of > 0.05.upsilon.M. I are useful as ***prodrugs*** , competitive inhibitors of trypsinlike proteases, such as thrombin, and in particular in the treatment of conditions where inhibitors of thrombin is required (e.g. ***thrombosis***) or as anticoagulants.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 9 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001301777 MEDLINE
DOCUMENT NUMBER: 21127175 PubMed ID: 11228340
TITLE: The direct thrombin inhibitor melagatran and its oral prodrug H 376/95: intestinal absorption properties, biochemical and pharmacodynamic effects.
AUTHOR: Gustafsson D; Nystrom J; Carlsson S; Bredberg U; Eriksson U; Gyzander E; Elg M; Antonsson T; Hoffmann K; Ungell A; Sorensen H; Nagard S; Abrahamsson A; Bylund R
CORPORATE SOURCE: Department of Cardiovascular Pharmacology, AstraZeneca R&D Molndal, S-431 83, Molndal, Sweden..
david.gustafsson@astrazeneca.com
SOURCE: THROMBOSIS RESEARCH, (2001 Feb 1) 101 (3) 171-81.
Journal code: 0326377. ISSN: 0049-3848.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010604
Last Updated on STN: 20010604
Entered Medline: 20010531
AB Suboptimal gastrointestinal absorption is a problem for many direct ***thrombin*** ***inhibitors*** . The studies presented herein

describe the new oral direct ***thrombin*** ***inhibitor*** H 376/95, a ***prodrug*** with two protecting residues added to the direct ***thrombin*** ***inhibitor*** ***melagatran*** . Absorption properties in vitro: H 376/95 is uncharged at intestinal pH while ***melagatran*** is charged. H 376/95 is 170 times more lipophilic (octanol water partition coefficient) than ***melagatran*** . As a result, the permeability coefficient across cultured epithelial Caco-2 cells is 80 times higher for H 376/95 than for melagtran. Pharmacokinetic studies in healthy volunteers: H 376/95 is converted to ***melagatran*** in man. Oral bioavailability, measured as ***melagatran*** in plasma, is about 20% after oral administration of H 376/95, which is 2.7-5.5 times higher than after oral administration of ***melagatran*** . The variability in the area under the drug plasma concentration vs. time curve (AUC) is much smaller with oral H 376/95 (coefficient of variation 20%) than with oral ***melagatran*** (coefficient of variation 38%). Pharmacodynamic properties: H 376/95 is inactive towards human alpha-thrombin compared with ***melagatran*** [inhibition constant (K(i)) ratio, 185 times], a potential advantage for patients with silent gastrointestinal bleeding. In an experimental ***thrombosis*** model in the rat, oral H 376/95 was more effective than the subcutaneous low molecular weight heparin dalteparin in preventing ***thrombosis*** . Conclusion: By the use of the ***prodrug*** principle, H 376/95 endows the direct ***thrombin*** ***inhibitor*** ***melagatran*** with pharmacokinetic properties required for oral administration without compromising the promising pharmacodynamic properties of ***melagatran*** .

L8 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:772474 CAPLUS
DOCUMENT NUMBER: 133:340244
TITLE: A pharmaceutical formulation comprising a low molecular weight thrombin inhibitor and its prodrug
INVENTOR(S): Gustafsson, David
PATENT ASSIGNEE(S): Astrazeneca AB, Swed.
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000064470	A1	20001102	WO 2000-SE756	20000419
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
SE 9901442	A	20001022	SE 1999-1442	19990421
BR 2000009847	A	20020108	BR 2000-9847	20000419
EP 1200118	A1	20020502	EP 2000-928047	20000419
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
NO 2001005107	A	20011019	NO 2001-5107	20011019

PRIORITY APPLN. INFO.: SE 1999-1442 A 19990421
SE 1999-4419 A 19991203
WO 2000-SE756 W 20000419

OTHER SOURCE(S): MARPAT 133:340244
AB A pharmaceutical formulation contains a low mol. wt. ***thrombin*** ***inhibitor*** , or a pharmaceutically acceptable deriv. with an adjuvant, diluent or carrier; a pharmaceutical formulation including a ***prodrug*** of a low mol. wt. ***thrombin*** ***inhibitor*** , or a deriv. of that ***prodrug*** , in admixt. with an adjuvant, diluent or carrier. The formulation is suitable for administration in the treatment of a condition in which the inhibition of thrombin is required. A controlled, randomized, parallel group, Swedish multi-center pilot study was carried out. The study was open with regard to the drugs under

evaluation but was blind for the patients, all personnel at the study sites, and for the person monitoring the expts. with regard to the doses of ***melagatran*** and the ***prodrug*** of ***melagatran***, EtOOC-CH2-(R)Cgl-Aze-Pab-OH (I). A combination of s.c. administered ***melagatran*** and orally administered I is effective in preventing venous ***thrombosis*** after orthopedic surgery.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:742118 CAPLUS
DOCUMENT NUMBER: 133:310144
TITLE: Preparation of amidine-terminated peptides as prodrugs of thrombin inhibitors
INVENTOR(S): Baucke, Dorit; Mack, Helmut; Seitz, Werner; Hornberger, Wilfried; Backfisch, Gisela; Delzer, Jurgen
PATENT ASSIGNEE(S): BASF A.-G., Germany
SOURCE: PCT Int. Appl., 136 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000061609	A2	20001019	WO 2000-EP3009	20000405
WO 2000061609	A3	20010315		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1165601	A2	20020102	EP 2000-920661	20000405
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 2000009674	A	20020115	BR 2000-9674	20000405
NO 2001004875	A	20011113	NO 2001-4875	20011008

PRIORITY APPLN. INFO.:
DE 1999-19915930 A 19990409
DE 1999-19934123 A 19990723
DE 1999-19947920 A 19991006
WO 2000-EP3009 W 20000405

OTHER SOURCE(S): MARPAT 133:310144
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention concerns prepn. of title compds., e.g. (I), which act as prodrugs for competitive inhibitors of trypsin-type serin proteases, esp. thrombin and kininogenases such as kallikrein, for use in treatment of disease or as thrombin inhibitors, anticoagulants and anti-inflammatory agents. Extensive examples of prepn. of precursors, e.g. (II) or (III), are given. In in vitro tests of oral resorption rate using human colon adenocarcinoma cells grown on polycarbonate membranes, I had very good transport characteristics. Substances were also tested in rats for effect on ecarin clotting times, activated partial thromboplastin times, and thrombin times (no data).

L8 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:742090 CAPLUS
DOCUMENT NUMBER: 133:296664
TITLE: Preparation of peptide amidine analogs as prodrugs of thrombin inhibitors
INVENTOR(S): Baucke, Dorit; Mack, Helmut; Seitz, Werner;

Hornberger, Wilfried; Backfisch, Gisela; Delzer, Jurge[illegible]
PATENT ASSIGNEE(S): BASF A.-G., Germany
SOURCE: PCT Int. Appl., 72 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000061577	A1	20001019	WO 2000-EP3008	20000405
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
BR 2000009653	A	20020108	BR 2000-9653	20000405
EP 1169318	A1	20020109	EP 2000-915197	20000405
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
NO 2001004807	A	20011204	NO 2001-4807	20011003

PRIORITY APPLN. INFO.: DE 1999-19915930 A 19990409
DE 2000-10006799 A 20000215
WO 2000-EP3008 W 20000405
OTHER SOURCE(S): MARPAT 133:296664
GI

/ Structure 2 in file .gra /

AB The present invention relates to prodrugs of general formula (I) (see document for definitions), useful as prodrugs with improved adsorption for in vivo compds. which are competitive inhibitors of trypsin-like serine proteases, esp. thrombin. Thus, reacting N-(CH2C(O)OC(CH3)3)(C(O)OC(CH3)3)-D-cyclohexylalanine (prepn. given) and 3,4-dehydro-L-proline Me ester hydrochloride led to an intermediate which, following a previous Patent synthesis (WO 96/25326), was converted to the cyano precursor of (II), which was reacted with H2NOH and NH3, to give the hydroxyamidine compd. In in vitro transport expts., II showed very good transport. In in vivo pharmacokinetic tests using rats and dogs, the compds. themselves had poor thrombin-inhibiting action, but acted as prodrugs which, through metab., led to active compds. (no data).
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:506597 CAPLUS
DOCUMENT NUMBER: 127:136080
TITLE: Preparation of peptide derivatives as prodrugs of thrombin inhibitors
INVENTOR(S): Antonsson, Thomas; Gustafsson, David; Hoffmann, Kurt-Jurgen; Nystrom, Jan-Erik; Sorensen, Henrik; Sellen, Mikael
PATENT ASSIGNEE(S): Astra Aktiebolag, Swed.; Antonsson, Thomas; Gustafsson, David; Hoffmann, Kurt-Jurgen; Nystrom, Jan-Erik; Sorensen, Henrik; Sellen, Mikael
SOURCE: PCT Int. Appl., 94 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

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     WO 9723499         A1   19970703       WO 1996-SE1680   19961217
         W:  AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,
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             LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT,
             RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN,
             AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR,
             IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML,
             MR, NE, SN, TD, TG
     ZA 9610353         A    19970623       ZA 1996-10353    19961209
     CA 2238737         AA   19970703       CA 1996-2238737  19961217
     AU 9712178         A1   19970717       AU 1997-12178    19961217
     AU 706350          B2   19990617
     EP 869966          A1   19981014       EP 1996-943446   19961217
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO
     CN 1209139         A    19990224       CN 1996-180024   19961217
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     EP 995755          A1   20000426       EP 1999-120315   19961217
     EP 995755          B1   20010816
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO
     JP 2001089498      A2   20010403       JP 2000-220423   19961217
     AT 204292          E    20010915       AT 1999-120315   19961217
     RU 2176644         C2   20011210       RU 1998-111148   19961217
     ES 2163916         T3   20020201       ES 1999-120315   19961217
     US 5965692         A    19991012       US 1997-776231   19970131
     NO 9802809         A    19980820       NO 1998-2809     19980618
     US 6262028         B1   20010717       US 1999-353644   19990715
     US 2002142968      A1   20021003       US 2002-74008    20020214
PRIORITY APPLN. INFO.:                  GB 1995-26273    A  19951221
                                        SE 1996-556      A  19960215
                                        EP 1996-943446   A3 19961217
                                        JP 1997-523571   A3 19961217
                                        WO 1996-SE1680   W  19961217
                                        US 1997-776231   A1 19970131
                                        US 1999-353644   A1 19990715
                                        US 2000-708449   B1 20001109
OTHER SOURCE(S):         MARPAT 127:136080
AB   Title compds. of formula R1O(O)C-CH2-(R)Cgl-Aze-Pab-R2 [wherein R1 = H,
     C1-10 alkyl, (un)substituted C1-3 alkylphenyl, A1C(O)N(R3)R4, A1C(O)OR3;
     (R)Cgl = (R)-cyclohexyl glycine; Aze = (S)-azetidine-2-carboxylic acid;
     Pab = 1-amidino-4-aminomethylbenzene; R2 (which replaces one of the
     hydrogen atoms in the amidino unit of Pab) = OH, OC(O)R5, C(O)OR6,
     C(O)OCH(R7)OC(O)R8; R3 and R4 are independently e.g., H, C1-6 alkyl, Ph,
     or together with the nitrogen atom represent pyrrolidinyl or piperidinyl;
     R5 = C1-17 alkyl, Ph, or 2-naphthyl (all of which are optionally
     substituted by C1-6 alkyl or halogen); R6 = (un)substituted 2-naphthyl,
     Ph, C1-3 alkylphenyl, C1-12 alkyl; R7 = H, C1-4 alkyl; R8 = e.g.,
     2-naphthyl, Ph, C1-6 alkoxy, (un)substituted C1-8 alkyl] or a
     pharmaceutically acceptable salt thereof, which are useful as prodrugs of
     inhibitors of trypsin-like proteases (no data), such as thrombin, and in
     particular in the treatment of conditions where inhibition of thrombin is
     required (e.g. thrombosis) or as anticoagulants, were prepd.  For example,
     EtO2C-CH2-(R)Cgl-Aze-Pab-COOCH2CH:CH2 was prepd. via coupling of
     Me3CO2C-(R)Cgl-Aze-Pab-H with allyl chloroformate followed by Boc
     deprotection and coupling with Et bromoacetate.  The title compds. were
     all found to exhibit oral and/or parenteral bioavailability in rats as the
     active inhibitor HO2C-CH2-(R)Cgl-Aze-Pab-H, either as the free acid and/or
     as one or more ester thereof.


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     (FILE 'HOME' ENTERED AT 16:48:24 ON 24 NOV 2002)

     FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
     16:48:53 ON 24 NOV 2002
L1         10243 S THROMBIN INHIBITOR
L2            50 S L1 (P) PRODRUG
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L3              0 S L2 (P) (KIT OR COMPOSITION)
L4             29 S MELAGATRAN (P) PRODRUG
L5              1 S L4 (P) (KIT OR COMPOSITION OR FORMULATION)
L6         309321 S THROMBOSIS OR (PULMONARY EMBOLISM) OR (DISSEMINATED INTRAVASC
L7             14 S L6 (P) (L2 OR L4)
L8              9 DUPLICATE REMOVE L7 (5 DUPLICATES REMOVED)

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COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                      ENTRY    SESSION
FULL ESTIMATED COST                                   48.11      48.32

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                      ENTRY    SESSION
CA SUBSCRIBER PRICE                                   -4.34      -4.34

STN INTERNATIONAL LOGOFF AT 16:54:07 ON 24 NOV 2002
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